REMARKS

Claims 7-32 are pending in the application as shown in the paper filed August 22, 2005. Claims 30-32 have been withdrawn as being drawn to non-elected species. Claims 7-29 are under active consideration.

A new Sequence Listing setting forth the sequence of SEQ ID NO:5 is filed concurrently herewith. SEQ ID NO:5 is disclosed in GenBank Accession No. M57244 as the sequence of the plasmid EWD299 disclosed in the instant application, for example, at page 41, line 35. In addition, the paragraph on page 41, beginning at line 35 is amended to include the sequence identifier, SEQ ID NO:5, in reference to the plasmid EWD299. No new matter is added by way of these amendments to the specification or by way of presentation of this Sequence Listing. The Examiner is respectfully requested to enter the Sequence Listing and these amendments to the specification.

Objection to the Drawings

Fig. 12 remains objected to on the grounds that the figure and corresponding amendments to the specification allegedly "introduced new matter" (Final Office Action, pages 2-3. In particular, the Final Office Action alleges that "the original disclosure does not support the showing of sequences as presented on Fig. 12" (Final Office Action, page 2). The Final Office Action further alleges:

> Applicant cites MPEP 608.01(p).2 as instructing to amend the disclosure to include material incorporated by reference. This part of MPEP 608.01(p), however, addresses whether filing date of an application wherein essential material is improperly incorporated by reference will be affected because of the reference.
> (Final Office Action, page 3.)

The Final Office Action also alleges:

> Second, nowhere in the specification applicant indicated possession of mutants of the particular sequences described in the Domenighini reference. The Domenighini reference itself is used in specification not to direct to particular sequences, but to direct to one particular residue of interest that this suggestion suggests to mutate. The disclosure as filed addresses strains of LT in general (p. 5, lines 5-7) and does not reduce the genus to particular species addressed in Domenighini. Applicant reiterates the specification, p. 5, lines 25-31, to argue that the specification cites the reference to show full-length sequences of LT-A proteins. Examiner, again, disagrees: the only mention of the Domenighini reference is to point that "residue to be mutated is that which

> corresponds to Ala-72 as defined for LT-A in Domenighini (p. 5, lines 27,28) to point at location of the Ala residue, not to a particular sequence. (Final Office Action, page 4.)

For the reasons of record, Applicants reiterate their position that FIG. 12 does not add new matter.

First, Applicants respectfully disagree that MPEP 608.01(p) only addresses whether the filing date of an application, improperly incorporating essential material by reference, is affected because of the reference. MPEP 608.01(p) specifically states that the filing date is unaffected and that "applicant will be required to amend the specification to include the material incorporated by reference." Thus, the amendment of the specification to include the material in FIG. 12 is proper and does not constitute new matter.

Second, the specification clearly describes the invention as encompassing polynucleotides encoding immunologically effective detoxified *E. coli* heat labile toxin (LT-A) polypeptides, wherein the amino acid residue corresponding to Ala-72 is substituted with an arginine residue. See specification, *e.g.*, at page 3, line 36 through page 3, line 3; page 5, lines 35-37; page 7, lines 20-21; page 41, line 35 through page 42, line 38. The specification cites Domenighini to show full-length sequences of LT-A proteins that may serve as reference sequences and the residue to be mutated that corresponds to Ala-72 in the reference sequences. Figure 12 corresponds to Figures 1 and 2 of Domenighini, showing an alignment of various wild-type LT sequences. Applicants further note that the sequences of Domenighini and those added to the specification were publically available at the time of filing.

In summary, Applicants reiterate that the incorporation of material deemed essential from the reference of Domenighini et al. is proper according to M.P.E.P. § 608.01(p). Therefore, **no** new matter was added by the previous submission of FIG. 12 or corresponding amendments, and withdrawal of the objection to the drawings is respectfully requested.

Objection to the Specification

The Specification remains objected to under 35 U.S.C. § 132 on the grounds that the amendment filed 2/08/2005 allegedly introduced new matter in the disclosure. In particular, the Final Office Action alleges that "the listing of sequences SEQ ID Nos. 1-4 constitutes new

matter for the same reasons as their description in the form of Fig. 12 – see the preceding objection to the Drawings" (Final Office Action, page 5).

Applicants respectfully disagree for the reasons discussed above regarding the objection to FIG.12. Applicants reiterate that the incorporation of material from the reference of Domenighini et al. was proper according to M.P.E.P. § 608.01(p). Therefore, **no** new matter was added by the previous submission of FIG. 12 or the corresponding amendments, and withdrawal of the objection to the specification is respectfully requested.

35 U.S.C. § 112, first paragraph, Written Description

Claims 7-29 remain rejected under 35 U.S.C. § 112, first paragraph for alleged lack of an adequate written description. Claim 8 has been canceled; therefore, the rejection with respect to this claim is moot. In particular, the Final Office Action alleges:

> There is no description of polypeptide comprising SEQ ID No. 1 with a mutated Ala72 residue as now claimed. Specification does address Arg72 mutant of an LT-A polypeptide in general (p. 41,42, for example, demonstrates method of making) but does not demonstrate possession of a particular polypeptide SEQ ID No. 1 as now claimed. (Final Office Action, page 5.)

The Final Office Action further alleges:

> Note that all Domenighini reference was used for – in the much recited section of specification (p. 5, lines 25-31) – is to point that "residue to be mutated is that which corresponds to Ala-72 as defined for LT-A in Domenighini (p. 5, lines 27,28), i.e., to point at location of the Ala residue, not to a particular sequence. Nowhere does specification as filed demonstrates possession polypeptide SEQ ID No. 1 or polynucleotides encoding thereof. Neither there is a description of polynucleotides of conjugates addressed in claims 8-9. (Final Office Action, page 6.)

Applicants respectfully traverse the rejection under 35 U.S.C. § 112, first paragraph on the following grounds.

It is well-settled law that the fundamental factual inquiry in written description is whether the specification conveys with reasonable clarity to those skilled in the art that, as of the filing date sought, applicant was in possession of the invention as now claimed. See, e.g., *Vas Cath, Inc. v. Mahurkar*, 935 F.2d 1557, 19 USPQ2d 1111. Determining whether the written description requirement is satisfied is a question of fact and the burden is on the Examiner to provide evidence as to why a skilled artisan would not have recognized that the applicant was in

possession of the claimed invention at the time of filing. *Vas Cath, Inc. v. Mahurkar*, 19 USPQ2d 1111 (Fed. Cir. 1991); *In re Wertheim*, 191 USPQ 90 (CCPA 1976). It is not necessary that the application describe the claimed invention *in ipsis verba*. Rather, all that is required is that the specification reasonably convey possession. See, *e.g.*, *In re Lukach*, 169 USPQ 795, 796 (CCPA 1971).

Indeed, in the recent case of *Capon v. Eshhar* 76 USPQ2d 1078 (CA FC 2005), the Federal Circuit completely rejected the notion that the specification must describe information (*e.g.*, nucleotide sequence) that is either known or can readily be determined based on scientific facts (Capon at page 1085):

> The "written description" requirement must be applied in the context of the particular invention and the state of the knowledge. The Board's rule that the nucleotide sequences of the chimeric genes must be fully presented, although the nucleotide sequences of the component DNA are known, is an inappropriate generalization. When the prior art includes the nucleotide information, precedent does not set a *per se* rule that the information must be determined afresh. Both parties state that a person experienced in the field of this invention would know that these known DNA segments would retain their DNA sequences when linked by known methods. Both parties explain that their invention is not discovering which DNA segments are related to the immune response, for that is in the prior art, but in the novel combination of the DNA segments to achieve a novel result.
>
> The "written description" requirement states that the patentee must describe the invention; it does not state that every invention must be described in the same way. As each field evolves, the balance also evolves between what is known and what is added by each inventive contribution.

Thus, there is no requirement to re-describe sequences that are already known. The claimed subject matter, that is, polynucleotides encoding an immunologically effective detoxified *E. coli* heat labile toxin (LT-A) polypeptide, wherein the amino acid residue corresponding to Ala-72 of SEQ ID NO:1 is an arginine residue, is adequately described in the specification. Applicants again direct the Examiner's attention to page 5, lines 25-31 and page 41, lines 35-38 of the specification, describing sources of LT-A-encoding sequences and the site of the arginine substitution (*e.g.*, citing Domenighini et al., Pronk et al and Spicer et al.). Further, it is well within the purview of a skilled artisan to align sequences with SEQ ID NO:1; to determine which residue corresponds to Ala-72; and to substitute an arginine for this residue.

(See, *e.g.*, page 42 of the specification). Methods of including these polynucleotides in vectors, host cells and the like are similarly described in the specification and within the purview of the skilled artisan. (See, *e.g.*, pages 6-8 and 19 to 43 of the specification). Therefore, the skilled artisan, having followed the teaching of the specification, would have no doubt that Applicant was in possession of the claimed subject matter.

With regard to the assertion that the specification only addresses Arg72 mutants of LT-A polypeptides in general, particularly at pages 41 and 42, Applicants respectfully disagree. Applicants specifically describe the preparation of an LT-A72R mutant by using the plasmid EWD299 encoding the LT-A sequence presented herein as SEQ ID NO:5 (see specification at page 41, lines 35-36). Applicants note that the nucleotide sequence of the plasmid pEWD299 and the amino acid sequence of the LT-A polypeptide encoded by the plasmid pEWD299 were well known to one of skill in the art at the time of filing of the instant application, and the sequence of SEQ ID NO:5, in particular, was publicly available on August 20, 1994 in the NCBI database, well before the filing date of the instant application (see GenBank Accession No. M57244 attached at Exhibit A). Applicants clearly refer to the LT-A sequence of pEWD299 in the instant specification (see page 41, lines 34-38). Therefore, Applicants have, accordingly, submitted a Sequence Listing setting forth the sequence of SEQ ID NO:5. The preparation of polynucleotides further comprising an antigen or LT-B sequence, as recited in claims 8 and 9, respectively, is also adequately described. See the specification, for example, at page 5, lines 20-23; page 7, lines 23-24; page 13, lines 3-6; page 42, lines 11-16.

For at least the above reasons, Applicants respectfully request that the written description rejection under 35 U.S.C. § 112, first paragraph be withdrawn.

CONCLUSION

In light of the above remarks, Applicants submit that the present application is fully in condition for allowance. Early notice to that effect is earnestly solicited.

If the Examiner contemplates other action, or if a telephone conference would expedite allowance of the claims, Applicants invite the Examiner to contact the undersigned.

The Commissioner is hereby authorized to charge any fees and credit any overpayment of fees which may be required under 37 C.F.R. §1.16, §1.17, or §1.21, to Deposit Account No. 18-1648.

Please direct all further written communications regarding this application to:

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Respectfully submitted,

Date: December 21, 2005

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Enclosures:

1. Appendix A: GenBank Accession No. M57244

Appendix A


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LOCUS       EWDLTA                    723 bp    DNA     linear   BCT 23-APR-1996
DEFINITION  Plasmid EWD 299 (from E.coli) heat-labile enterotoxin subunit A
            (LT-A) gene, 3' end.
ACCESSION   M57244 J05702
VERSION     M57244.1  GI:531190
KEYWORDS    enterotoxin; heat-labile enterotoxin.
SOURCE      Plasmid EWD 299
  ORGANISM  Plasmid EWD 299
            other sequences; plasmids.
REFERENCE   1  (bases 1 to 723)
  AUTHORS   Tsuji,T., Inoue,T., Miyama,A., Okamoto,K., Honda,T. and Miwatani,T.
  TITLE     A single amino acid substitution in the A subunit of Escherichia
            coli enterotoxin results in a loss of its toxic activity
  JOURNAL   J. Biol. Chem. 265 (36), 22520-22525 (1990)
   PUBMED   2266142
COMMENT     On Aug 20, 1994 this sequence version replaced gi:148531.
            Original source text: Plasmid EWD 299 DNA.
FEATURES             Location/Qualifiers
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                     /organism="Plasmid EWD 299"
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ORIGIN
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      181 tccacttctc ttagtttgag aagtgctcac ttagcaggac agtctatatt atcaggatat
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      361 tattctcaga tatatggatg gtatcgtgtt aattttggtg tgattgatga acgattacat
      421 ggtaacaggg aatatagaga ccggtattac agaaatctga atatagctcc ggcagaggat
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      721 tga
//
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Dec 8 2005 13:13:13